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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,959	10/04/2000	Glenn Friedrich	LEX-0051-USA	9566

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/680,959	FRIEDRICH ET AL.	
	Examiner	Art Unit	
	Thái-An N. Ton	1632	

-- The MAILING DATE of this communicati n appears n the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/7/03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *07 July 2003* is: a)☐ approved b)☒ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendment, filed July 7, 2003, Paper No. 15, has been entered. Claims 3 and 7 have been amended. Claims 1-7 are pending and under current examination.

Any rejection made of record in the prior Office action, mailed 1/30/03, Paper No. 13, and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

Specification

The substitute specification, filed July 7, 2003, has been received. The specification has not been entered because Applicants have not provided the following: the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

The objection of the specification is maintained because the substitute specification has not been entered. The specification contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See p. 4, line 29.

Drawings

The drawings, filed July 7, 2003, have been received. However, Applicant has provided no statement to enter them into the instant Application. Appropriate correction is required.

Claim Rejections – 35 USC §101 & 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The prior rejection of claims 1-7 under 35 U.S.C. 101 is *maintained* because the claimed invention lacks patentable utility due to its not being not supported by either a specific and/or substantial utility or a well established utility for reasons of record advanced on pages 4-8 of the prior Office action.

The claimed genetically engineered mammalian cell lines which have been mutated by a process comprising the insertion of a recombinantly manipulated polynucleotide sequence into a gene, said gene corresponding to SEQ ID NO: 125, and isolated mouse embryonic stem cell lines comprising an engineered retroviral gene trap vector in at least one gene comprising a polynucleotide sequence disclosed in SEQ ID NO: 125, are not supported by a specific asserted utility because the disclosed uses of the cell lines are not specific, and are generally applicable to any cell comprising any nucleic acid.

Applicants traverse the rejection. Applicants argue that the specifically described novel ES cell clones are each specifically identified by corresponding exon sequences that provide a unique and highly specific resource for mapping that portion of the murine genome that encodes the described exon sequence and, by proxy, that portion of the human genome that encodes the human ortholog of the described sequences. See p. 3, of the Response. Applicants ask the Examiner to consider the public and private funds spend to obtain the human genomic sequence, and that one can state that such genomic sequence data, in part or in whole, have demonstrated a substantial and specific utility. See pp. 3-4, bridging ¶. Applicants argue that given that there can be no question that the final product of the claimed invention has a substantial pharmaceutical utility, there can be no question that the presently claimed murine ES cell clones have a substantial, credible and well established utility. Applicants argue that those of skill in the art would clearly understand that the described cells having an engineered mutation in the gene encoding SEQ ID NO: 125 [dystrobrevin B gene] would be suited to determine the *in* vivo function of the gene and that those skilled in the art would clearly not believe that any cell comprising a nucleic acid is equally well suited to identifying the *in vivo* function of the dystrobrevin B gene. See p. 4 of Applicants' Response. Applicants request that the Examiner consider the broader scientific acceptance of the inherent value of knockout mice to discovering the function of genomic sequence information. Applicants provide comments from the Albert Lasker award and point

to guidance from the National Institutes of Health, which issued a request for applications entitled Tools for Insertional Mutagenesis in the Mouse to support that the claimed invention has a well-established utility. See pp. 5-9 of the Response.

Applicants' arguments have been carefully considered, but they are not found to be persuasive. The fact that scientists have received the Lasker award for their technology or methodology does not render the products of that technique patentable. The fact that Applicant has produced particular mouse ES cell lines does not mean that Applicant have described the breadth of what the claims encompass. While those of ordinary skill may use Applicants' technique(s) or methodologies to study genes, they are not using Applicants' particularly claimed cell having the particular sequence mutated (*i.e.*, SEQ ID NO: 125). The claimed cell line has no well-known use in the absence of further characterization of the cell line itself. Furthermore, the arguments presented by Applicant are not relevant to the instant rejection. While the techniques of gene trapping and generating mutations in ES cells are necessary in revealing important genes for further research, cell lines which harbor mutations in uncharacterized genes have no patentable utility without knowing the identity and function of the gene in question.

The instant invention appears to be an invitation for trial and error experimentation to determine the specific function of the protein product encoded by the claimed nucleotide sequences, and from there to determine uses based upon

that function. In *Brenner*, the Court held that materials to be used as an object of research or methods of using those materials as an object for research have raised issues as to whether those materials possess a real world context to use of substantial utility. See Brenner v. Manson, 148 USPQ (US SupCt 1966).

The whole of the specification is directed to taking the cell line generated by the gene trapping technique and determining what the identity and function of a particular gene-trapped gene is, so to *potentially* provide useful information for therapeutic or diagnostic applications. The evidence of record at the time the claimed invention was filed did not disclose the identity or function of the gene comprising SEQ ID NO: 125.

Applicants argue that the presently claimed mouse ES cell clones provide a specific resource for discovering the *in vivo* function of a specific human ortholog. Applicants argue that when the ES cells having the mutation in the gene corresponding to SEQ ID NO: 125 were used to produce homozygous mutant animals, male animals homozygous for the mutated allele displayed a substantially reduced percentage of total body fat. Applicants argue that the indication of this overt phenotype indicates that this gene represents one of the small percentage of genes that encode proteins that present an overt commercial opportunities for pharmaceutical development, and that this is demonstrated pharmaceutical utility satisfies utility guidelines.

In response, the mouse described in Applicants' arguments fails to be taught in the instant specification. Nowhere does the specification teach the generation of mice from ES cells comprising an engineered mutation in a gene comprising SEQ ID NO: 125, and the resulting phenotype. Without evidence of record in the specification showing the mouse, which displays a substantially reduced percentage of total body fat, Applicants' arguments fail to support a use for the claimed ES cells. It would require further experimentation to determine what the direct or indirect effects of mutating the gene comprising SEQ ID NO: 125. Thus, the evidence of record fails to support the asserted utility of the claimed ES cells to produce an animal because this is a non-specific use that is applicable to any embryonic stem cell. It is further noted that the specification as filed fails to teach or provide evidence that SEQ ID NO: 125 corresponds to the human gene dystrobrevin B. As such, Applicants arguments of the specific use of the claimed invention in therapeutic intervention in the fields of obesity and metabolism are not supported by the specification.

It is reiterated that the claimed cells and embryonic stem cell is not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, the stem cell could be used to generate a transgenic animal, and the resulting transgenic animal could be studied to see the effect of the introduced mutation. The need for such research clearly indicates that the claimed cell is not disclosed as to a currently available or

substantial utility. A starting material that can only be used to produce a final product does not have substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In the instant case, none of the cells or transgenic animals that are to be produced as final products have asserted or identified specific and substantial utilities. Identifying and studying the properties of an embryonic stem cell or transgenic animal does not define a "real world" context or use. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed, nor any art of record discloses or suggests any property or activity for the claimed embryonic stem cells such that another non-asserted utility would be well-established.

Accordingly, it is maintained that the claimed mouse ES cells lack a specific and substantial utility until the gene is further characterized and identified as to its function. No genotype nor phenotype of record is associated with SEQ ID NO: 125 and no gene function (or disruption thereof) is disclosed for any gene comprising the nucleotide sequence set forth in SEQ ID NO: 125. The claimed product cannot be considered a research tool, but rather, is a material to be experimented upon. Note that Applicants' arguments focus on future uses based upon information that is not presently at hand.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1-7 under 35 U.S.C. 112, first paragraph is *maintained* for reasons of record. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The prior rejection of claims 1-7 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection is maintained for reasons of record.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art **as of Applicants effective filing date**. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Applicants traverse the rejection. Applicants argue that those of skill in the art would clearly understand that the sequence data reported in SEQ ID NO: 125 represent an exon sequence that clearly identifies the gene that has been mutated in the described ES cell line (in this case the beta-dystrobrevin gene as identified in Figure 2). Applicants argue that those of skill in the art would understand that Applicants are in actual possession of ES cell clones because those of skill in the art would understand that actual possession of ES cell clones is a prerequisite of obtaining the exon sequence data reported in SEQ ID NO: 1. See p. 10 of the Response.

Applicants' arguments have been considered, but are not found to be persuasive. Applicant is not considered to be in possession of the gene encoded by SEQ ID NO: 125. Applicants' argument is analogous to the following scenario: that merely because a cell has been isolated, that one would have completely characterized it and is in possession of all of its properties. This is untrue. The isolated cell must have its properties determined just as Applicant must now perform further experimentation to determine the identity of the full length gene encoded by SEQ ID NO:1, and the functions thereof.

The specification discloses that SEQ ID Nos: 1-154 correspond to murine cDNA sequences. As it is not apparent that SEQ ID NO: 125 is a complete cDNA sequence, the claims read on all cells that have a disruption of a gene which is encoded by an undescribed sequence. Additionally, it is noted that SEQ ID NO: 125 is 414 nucleotides in length and contains at least 3 wild cards or unspecified nucleotides. Given the multiplicity of sequences encompassed by SEQ ID NO: 125, the specification does not describe what the actual sequence Applicants' cells or ES cell(s) possess, nor have they identified the particular gene associated with those DNA fragments. One of ordinary skill in the art would not know what actual sequence was present in the ES cells produced by Applicant.

The claims recite a genetically engineered mammalian cell that has been mutated by disruption of a gene, "identifiable as corresponding to SEQ ID NO: 125". This encompasses a large genera of sequences of which each of the each of the

sequences merely comprises SEQ ID NO: 125, in addition to other undescribed sequences that make up the claimed gene. For example, the specification fails to describe promoter sequences, intron/exon boundaries, or 5' and 3' UTR, for the breadth of the claims encompassing a large genera of sequences. Many, if not most, of the sequences encompassed may not be real sequences corresponding to real genes. The claims require that one of ordinary skill in the art produce murine ES cell lines, which comprises a disruption of a gene whose sequence may not exist in nature. The skilled artisan cannot envision the detailed chemical structures of all the sequences encompassed by the above noted SEQ ID No: 125.

Applicants argue that the clear phenotype manifested by mice produced from the described ES cell clones also knocks out any question of whether SEQ ID NO: 125 is indeed encoded by a gene whose sequence exists in nature. See p. 10 of Applicants' Response.

Applicants' arguments are not found to be persuasive. There is no evidence or teaching provided by the specification as filed to show the generation of mice with a resulting phenotype.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejection of claim 7 under 35 U.S.C. 112, second paragraph, is *maintained*, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants argue that those of skill in the art would realize that the mutation would be in a mouse gene encoding SEQ ID NO: 125, and that those of skill in the art would also recognize that mouse ES cells are typically diploid and thus contain at least two copies of each gene. The described mutation can occur in either of the two loci and be passed to offspring cells or animals. See p. 11 of Applicants' response.

Applicants' arguments have been considered but are not persuasive. The rejection is directed to the breadth of the claim. Particularly, the claim recites that the mouse embryonic stem cell line comprises "at least one gene comprising a polynucleotide sequence" [see lines 1-2 of the claim]. It is unclear if there is more than one gene encoded by the polynucleotide sequence, or that there is more than

one polynucleotide sequence disclosed in SEQ ID NO: 125. For example, many genes could comprise SEQ ID NO: 125 within their entire sequence.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)-872-9306.

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